

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

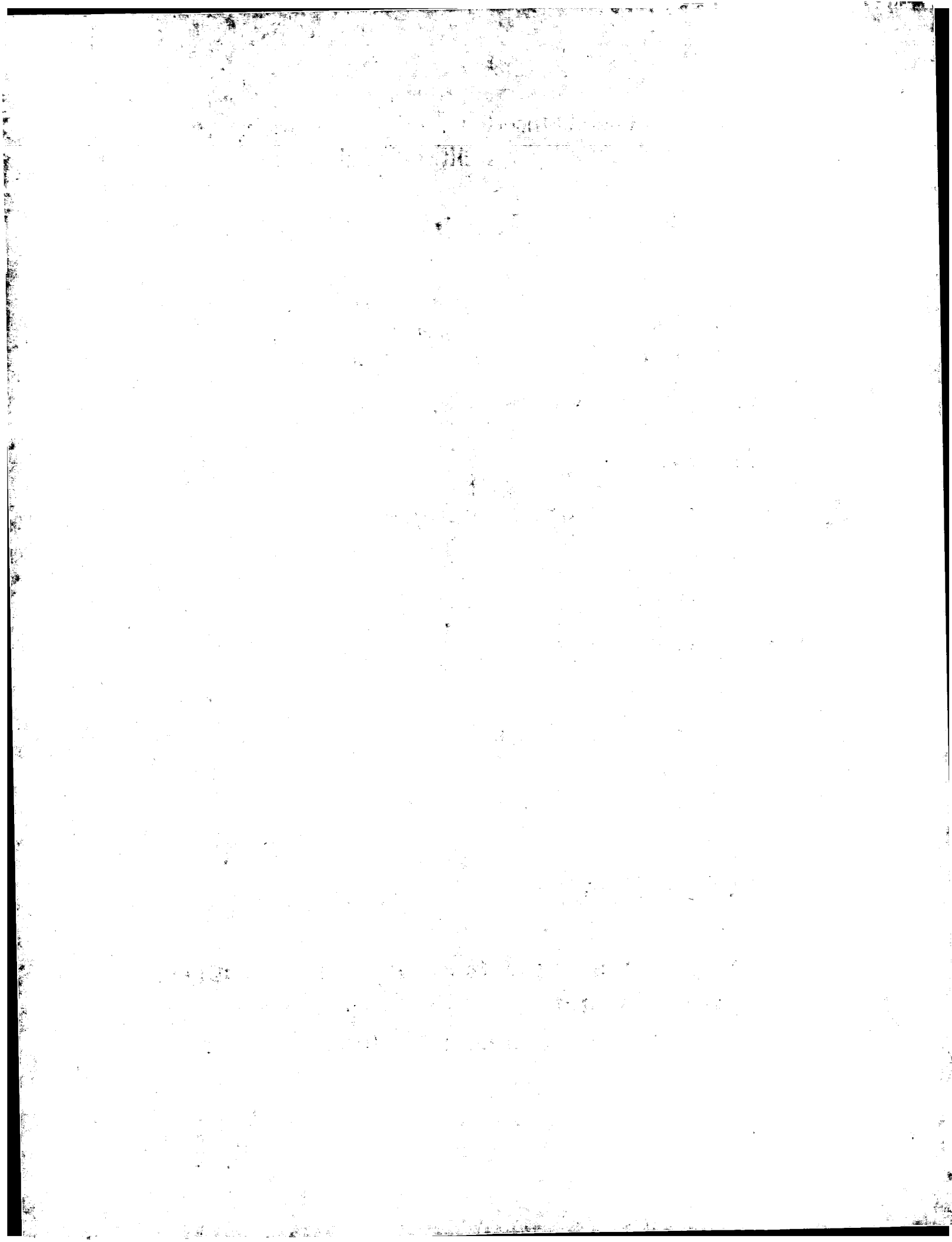
Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: A61M 31/00	A1	(11) International Publication Number: WO 98/20930 (43) International Publication Date: 22 May 1998 (22.05.98)
(21) International Application Number: PCT/US97/20480 (22) International Filing Date: 7 November 1997 (07.11.97) (30) Priority Data: 60/030,481 15 November 1996 (15.11.96) US (71) Applicant: ALZA CORPORATION [US/US]; 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US). (72) Inventors: DIONNE, Keith, E.; 4 Hancock Park, Cambridge, MA 02139 (US). LAUTENBACH, Scott, D.; 466 23rd Avenue, Forest Lake, MN 55025 (US). EFTIMIE, Antoaneta, C.; 1639 Canna Lane, San Jose, CA 95124 (US). LY, Kevin, S.; 828 Saraband Way, San Jose, CA 95122 (US). (74) Agents: CLARKE, Pauline, A. et al.; Alza Corporation, 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: OSMOTIC DELIVERY SYSTEM AND METHOD FOR ENHANCING START-UP AND PERFORMANCE OF OSMOTIC DELIVERY SYSTEMS		
(57) Abstract <p>The present invention relates to an osmotically driven agent delivery system for delivering a beneficial agent. The osmotic delivery system includes an osmotic agent which operates by imbibing fluid from an outside environment, causing the release of a beneficial agent. The osmotic delivery system includes a liquid or gel additive surrounding the osmotic agent for enhancing start-up and lubricating the osmotic agent. The liquid or gel additive is an incompressible lubricating fluid which fills any air gaps between the osmotic agent and the walls of a chamber and substantially reduces start-up delays.</p> <div data-bbox="941 1155 1429 1974"> </div>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

1 OSMOTIC DELIVERY SYSTEM AND METHOD FOR
2 ENHANCING START-UP AND PERFORMANCE OF
3 OSMOTIC DELIVERY SYSTEMS
4

5 BACKGROUND
6

7 1. Field of the Invention

8 The present invention relates to a delivery device for delivery of beneficial
9 agents at a controlled rate, and more particularly, the invention relates to osmotic drug
10 delivery systems and methods for enhanced start-up and performance of osmotic drug
11 delivery systems.
12

13 2. Description of the Related Art

14 Controlled delivery of beneficial agents, such as drugs, in the medical and
15 veterinary fields has been accomplished by a variety of methods. One method for
16 controlled and prolonged delivery of beneficial agents involves the use of osmotic
17 delivery systems. These devices can be implanted to release the beneficial agent in a
18 controlled manner over a preselected time or administration period. In general,
19 osmotic delivery systems operate by imbibing fluid from the outside environment and
20 releasing corresponding amounts of the beneficial agent.

21 Osmotic delivery systems, commonly referred to as "osmotic pumps,"
22 generally include some type of a capsule having walls which selectively pass water
23 into an interior of the capsule which contains a water-attracting osmotic agent. The
24 absorption of water by the water-attracting agent within the capsule reservoir creates
25 osmotic pressure within the capsule which causes the beneficial agent to be delivered
26 from the capsule. The water-attracting agent may be the beneficial agent delivered to
27 the patient; however, in most cases, a separate osmotic agent is used specifically for
28 its ability to draw water into the capsule.

29 When a separate osmotic agent is used, the osmotic agent may be separated
30 from the beneficial agent within the capsule by a movable dividing member or piston.

1 The structure of the capsule is such that the capsule does not expand when the
2 osmotic agent takes in water. As the osmotic agent expands, it causes the beneficial
3 agent to be discharged through an orifice at the same rate as the water enters the
4 osmotic agent by osmosis. Osmotic delivery systems may be designed to deliver a
5 beneficial agent at a controlled constant rate, a varying rate, or in a pulsatile manner.

6 In known osmotic delivery systems, an osmotic tablet is used as the osmotic
7 agent and is placed inside the capsule. The osmotically active agent and the
8 compartment in which it resides may be referred to as an "osmotic engine." A
9 membrane plug is then placed in an opening in the capsule through which the tablet
10 was inserted. The water enters the capsule through the membrane plug.
11 Alternatively, water may enter directly through the capsule walls if they are permeable
12 to water.

13 Due to machining and tableting tolerances, the osmotic tablet in the solid initial
14 state is generally sized somewhat smaller than the reservoir in which it is received.
15 Thus, there are air-filled gaps between the osmotic tablet and the surrounding walls of
16 the chamber, between the osmotic tablet and the membrane plug through which water
17 is absorbed, and between the osmotic tablet and the piston. Due to these air-filled
18 gaps, when water begins to be drawn into the osmotic tablet through the membrane
19 plug, the osmotic tablet expands into the surrounding air space and beneficial agent
20 delivery start-up is delayed by a time during which the osmotic tablet expands to fill
21 the air spaces within the chamber. The start-up may be delayed up to several days or
22 weeks depending on the size of the air gaps and the flow rate of the system. Delayed
23 start-up of beneficial agent delivery is a significant problem in osmotic delivery
24 systems.

25 Another potential problem with known osmotic delivery systems is freezing-up
26 or locking of the osmotic tablet against the sides of the chamber. The osmotic tablet
27 passes through several states from the solid initial state to the hydrated delivery state.
28 As the tablet begins to swell upon wetting it acts more like a solid than a deformable
29 gel. Upon initial wetting, the swelling of the tablet can cause it to lock against the
30 rigid capsule reservoir side walls causing the agent delivery to be delayed until

1 sufficient water has permeated into the osmotic tablet to soften the tablet to the point
2 where it flows. The freeze-up of the osmotic tablet upon initial wetting leads to
3 delayed delivery. In addition, freeze-up can also lead to catastrophic problems such as
4 membrane rupture, expulsion of the membrane plug, or a sudden increase in the
5 delivery rate of the beneficial agent.

6 Known osmotic delivery systems include those disclosed in U.S. Patent Nos.
7 3,797,492, 3,987,790, 4,008,719, 4,865,845, 5,057,318, 5,059,423, 5,112,614,
8 5,137,727, 5,151,093, 5,234,692, 5,234,693, 5,279,608, and 5,336,057. Pulsatile
9 delivery devices are also known which deliver a beneficial agent in a pulsatile
10 manner as disclosed in U.S. Patent Nos. 5,209,746, 5,308,348, and 5,456,679.
11 The disclosure of each of the above identified patents is hereby incorporated by
12 reference in its entirety to the same extent as if the language of each patent were
13 specifically and individually incorporated by reference.

14

15

SUMMARY OF THE INVENTION

16 The device according to the present invention addresses the disadvantages of
17 the prior art osmotic delivery systems by providing an osmotic engine and method
18 for enhancing start-up and performance of osmotic delivery systems. The osmotic
19 engine reduces start-up delays and prevents freeze-up of the osmotic agent.

20 According to one aspect of the present invention, an osmotic drug delivery
21 device includes a capsule including a first chamber for containing a beneficial agent
22 and a second chamber containing an osmotic agent, an at least partially fluid
23 permeable wall of the second chamber allowing fluid to pass from a surrounding
24 environment into the second chamber, and an incompressible fluid additive or filler
25 within the second chamber surrounding the osmotic agent.

26

BRIEF DESCRIPTION OF THE DRAWING FIGURES

The invention will be described in greater detail with reference to the accompanying drawings in which like elements bear like reference numerals, and wherein:

FIG. 1 is a side sectional view of an osmotic delivery device according to the present invention;

FIG. 2 is a graph illustrating the improved release rate of an osmotic delivery device according to the present invention; and

FIG. 3 is a graph illustrating the resulting improved release rates corresponding to different embodiments of the present invention which each include a different fluid additive.

DETAILED DESCRIPTION

The present invention relates to an osmotic drug delivery system for delivering a beneficial agent. The delivery system according to the present invention includes an additive for enhancing start-up and lubricating the osmotic agent.

FIG. 1 illustrates an example of an osmotic drug delivery device 10 according to the present invention. The configuration illustrated in FIG. 1 is one example of a drug delivery device and is not to be construed as limiting the present invention. The present invention is generally applicable to all osmotic delivery devices having any number of shapes, and to all such devices administered in any variety of methods such as oral, ruminal, and implantable osmotic delivery techniques.

The osmotic drug delivery device 10, as illustrated in FIG. 1, includes an enclosure or elongated substantially cylindrical capsule 12 having a first open end 14, and a second enclosed end 16. The closed end 16 has one or more fluid delivery orifices 18. The elongated capsule 12 is formed of a material which is sufficiently rigid to withstand expansion of an osmotic agent without changing size or shape. The elongated capsule 12 may also be largely impermeable to fluids in the

1 environment as well as to ingredients contained within the dispensing device such
2 that the migration of such materials into or out of the device through the
3 impermeable material is so low as to have substantially no adverse impact on the
4 function of the osmotic delivery device.

5 Within the capsule 12 is a first chamber 20 for containing a beneficial agent
6 to be delivered. Such a beneficial agent may optionally include pharmaceutically
7 acceptable carriers and/or additional ingredients such as antioxidants, stabilizing
8 agents, permeation enhancers, etc.

9 The embodiment of the present invention illustrated in FIG. 1 includes a
10 movable partition or piston 22. A second chamber 24 within the capsule 12 is
11 separated from the first chamber 20 by the movable piston 22. The second chamber
12 24 receives an osmotic agent, which in the embodiment of the present invention
13 depicted in FIG. 1 is one or more osmotic tablets 26. The osmotic tablet is initially
14 non-flowable and solid. Osmotic agents, specifically the osmotic tablet 26 of the
15 embodiment of the present invention illustrated FIG. 1, drive the osmotic flow of
16 osmotic delivery devices. The osmotic agent need not be a tablet; it may be other
17 conceivable shapes, textures, densities, and consistencies and still be within the
18 confines of the present invention. For example, the osmotic agent may be in the
19 form of a powder.

20 The movable piston 22 is a substantially cylindrically member which is
21 configured to fit within the capsule 12 in a sealed manner which allows the piston to
22 slide along a longitudinal direction within the capsule. The piston 22 may be in the
23 form of a slidable partition or a stationary and stretchable partition member. The
24 piston 22 preferably is formed of an impermeable resilient material and includes
25 annular ring shape protrusions 32 which form a seal with the inner surface of the
26 capsule. However, the present invention need not include the movable piston or
27 partition 22; in such an embodiment, the first chamber 24 and the second chamber
28 20 are separated by an interface between the osmotic agent 26 and the beneficial
29 agent. Thus, when the osmotic delivery system according to one embodiment of the
30 present invention is in use, the volumes of the first chamber 24 and the second

1 chamber 20 change as the osmotic agent 26 imbibes fluid from the surrounding
2 environment.

3 As illustrated in FIG. 1, the drug delivery device 10 of one embodiment of
4 the present invention includes a membrane plug 28 which is inserted in the open end
5 14 of the capsule 12 after placing the osmotic tablet 26 within the capsule. The
6 membrane plug 28 is formed of a semi-permeable material which allows fluid to
7 pass from an exterior fluid environment into the second chamber 24 to cause the
8 osmotic tablet 26 to swell. However, the semipermeable material forming the
9 membrane plug 28 is largely impermeable to the materials within the capsule and
10 other ingredients within the fluid environment.

11 The osmotic delivery device according to the present invention includes an
12 incompressible additive or filler within the second chamber 24 in the form of a
13 liquid or gel 30. The fluid 30 surrounds the osmotic tablet 26, fills the spaces
14 between the osmotic tablet and the chamber walls and displaces substantially all air
15 or gas within the second chamber, but does not cause the osmotic tablet to swell and
16 freeze-up.

17 In the embodiment described above, machining and tableting tolerances
18 require that there be an annular gap between the osmotic tablet 26 or tablets and the
19 surrounding capsule side walls. Small irregularities in the shape or contour of the
20 tablet 26 may also result in a gap between the osmotic tablet and the movable piston
21 22, and/or between the osmotic tablet and the membrane plug 28. These gaps which
22 are filled with air in the known drug delivery systems will vary in size from, for
23 example, between approximately 0.001 to 0.1 inches. Even the smallest of gaps can
24 cause a delay of several days to weeks before the delivery system begins to deliver
25 the beneficial agent. Additionally, air-filled gaps problematically affect the
26 beneficial agent delivery rate when an osmotic delivery system is subjected to
27 different external pressures, such as when a patient with an implanted device scuba
28 dives or travels to higher altitudes.

29 The fluid 30 which is provided within the second chamber 24 according to
30 the present invention displaces the air surrounding the osmotic tablet and improves

1 start-up time, which is the time from insertion of the device into the fluid
2 environment of use until the beneficial agent is actually delivered at a rate preferably
3 not less than approximately 70% of the intended steady-state or pulsating rate. For
4 example, the time to reach full delivery with a one year implantable osmotic drug
5 delivery system that does not use a fluid additive 30 according to the present
6 invention is about 30 days. Use of a fluid filler or additive 30 according to the
7 present invention shortens that period to less than about 15 days.

8 The fluid 30 is preferably an incompressible fluid which does not compress
9 upon swelling of the osmotic tablet. The incompressible fluid 30 reduces the start-
10 up time for the osmotic drug delivery device 10 because the delay during which the
11 osmotic tablet swells to fill the surrounding air space of the known devices is
12 eliminated. Furthermore, if the osmotic activity of the fluid 30 is selectively higher
13 than that of the osmotic agent or tablet 26, the addition of the fluid 30 may further
14 increase the initial and/or steady state delivery rate of the beneficial agent. In
15 general, the incompressible fluid additive 30 may be any liquid that is acceptable for
16 human implantation.

17 FIG. 2 illustrates the effect of the fluid additive 30 on the delivery of the
18 beneficial agent. FIG. 2 is a graph of the release rate over time comparing one
19 example of a delivery system according to the present invention with a delivery
20 system without a fluid additive. As shown in FIG. 2 the release rate of an osmotic
21 delivery system without an additive does not achieve the desired substantially
22 constant delivery rate of approximately 0.38 uL/day until about 35 days after
23 placing the capsule in the agent delivery environment. This 35 day time period for
24 the desired delivery rate to be achieved is the start-up period. In contrast, the start-
25 up period is substantially eliminated for an embodiment of the present invention
26 which includes a fluid additive or osmotic engine filler (PEG 400); the system takes
27 only about 5 to 10 days to reach the desired substantially constant delivery rate. In
28 addition, the beneficial agent delivery rate according to an embodiment of the
29 present invention, which includes the fluid additive 30, is more consistent

1 throughout the entire agent delivery period than the delivery rate of a system
2 without the fluid additive.

3 Furthermore, the beneficial agent delivery rate of an embodiment of the
4 present invention such as that illustrated in FIG. 1 is not affected by external
5 pressure changes of approximately +/- 0.5 atmospheres.

6 For a total test period of 190 days, the example of the present invention
7 illustrated in FIG. 2 has a start-up time of less than 10%, preferably less than 7%,
8 of the total administration period; the total administration period for the embodiment
9 of the present invention tested in FIG. 2 was one year. Although the test period for
10 the embodiment of the present invention tested in FIG. 2 was 190 days, and the total
11 administration period was 365 days, both may differ. The administration period is
12 typically predetermined and depends upon the particular application; for example,
13 the administration period is at least about one day, sometimes greater than 7 days,
14 often between about 30 days and 2 years, preferably greater than about 1 month,
15 and usually between about 1 month and 12 months.

16 FIG. 3 illustrates the effect of different fluid additives 30 on the delivery of
17 the beneficial agent. FIG. 3 is a graph of the release rate over time comparing
18 seven embodiments of osmotic delivery systems according to the present invention,
19 six of which each include a fluid additive which is not significantly absorbed by the
20 osmotic agent (PEG 400, PEG 1000, Tween 80, PG, DMSO, and peanut oil), and
21 one of which includes a fluid additive which is absorbed by the osmotic agent (6%
22 CMC in water). The release rates over time for the seven embodiments are
23 compared to a delivery system without a fluid additive (control).

24 As shown in FIG. 3, the start-up time for the control system is about 35
25 days, and is about 5 to 10 days for the embodiments of the present invention which
26 includes a fluid additive. FIG. 3 also illustrates that the release rate may be
27 selectively increased by using a predetermined fluid additive 30. For example, the
28 average release rate for an embodiment of the present invention including the Tween
29 80 additive is approximately .3 uL/day higher than that of an embodiment of the
30 present invention including the PEG 400 additive.

1 Furthermore, FIG. 3 illustrates that by using additives such as 6% CMC in
2 water, which is absorbed by the osmotic agent and leaves a lubricating film on the
3 exterior of the agent, the release rate may be dramatically increased while also
4 substantially eliminating the start-up period.

5 In addition to greatly improving the start-up period, the fluid 30 surrounding
6 the osmotic tablet 26 also acts as a lubricant to prevent the osmotic tablet 26 from
7 locking against the capsule side walls during initial wetting of the tablet. The
8 locking of the osmotic tablet 26 against the capsule side walls creates substantial
9 problems including freezing-up of the osmotic agent and pumping rate for a period
10 of time necessary to soften the tablet to a state at which it can flow. This problem is
11 particularly dramatic when the predetermined administration period must be short in
12 order to quickly deliver the beneficial agent. Locking of the osmotic tablet 26 may
13 also cause the membrane plug 28 to be dislodged or to rupture, and may cause
14 rupture of the capsule itself. In order to avoid these problems, a fluid filler or
15 additive 30 is preferably selected to surround and lubricate the osmotic tablet 26.

16 The fluid 30 which surrounds the osmotic tablet 26 in the osmotic drug
17 delivery system according to the present invention may be either a liquid or a gel.
18 The fluid 30 is preferably selected to be either a fluid which is not significantly
19 absorbed by the osmotic tablet, such as low molecular weight PEG's,
20 perfluorodecalin, Tween 80, Tween 20, PG, DMSO, or peanut oil. The fluid
21 additive 30 may also be a fluid which is absorbed by the osmotic tablet, leaves a
22 lubricating film on the exterior of the osmotic tablet, and prevents the system from
23 freezing-up, such as carboxymethyl cellulose/water gels.

24 The fluid 30 should not diffuse out of the system during normal storage. In
25 addition, the fluid 30 should be acceptable as an unarmful parenteral excipient
26 which could be delivered to the body in the event the capsule ruptures or breaks and
27 the fluid in the engine is exposed.

28 The fluid 30 should also be a fluid which does not diffuse out through the
29 membrane plug 28 during storage or react with the membrane plug, piston, or the

-10-

1 capsule itself. The fluid 30 is also selected so that contact with the fluid does not
2 change the permeability of the membrane plug.

3 Acceptable additives or fillers for use in the present invention include but are
4 not limited to polymers, such as polyethylene glycol (PEG) 400 and PEG 1000,
5 propylene glycol (PG), polyoxyethylene sorbitan monolaurate (Tween 20),
6 polyoxyethylene sorbitan monooleate (Tween 80), dimethyl sulfoxide (DMSO),
7 perfluorodecalin, silicone oils, organic liquids, and water or saline (if used with a
8 properly selected osmotic agent, such as 100% NaCl). The fluid additive or filler
9 may also be a gel, such as 6% carboxymethyl cellulose (CMC) in water.

10 Among the additives tested, the additives which resulted in engine freeze-up
11 include saturated NaCl solution, 1% CMC in water, water, 30% Tween 20 in
12 saline, and hydroxypropyl methylcellulose (HPMC) when used with the osmotic
13 tablet described below. For testing purposes, engine freeze-up occurred when
14 greater than 100 psi was needed to move the osmotic tablet. However, lower
15 pressures may be indicative of problematic freeze-ups during actual use of the
16 osmotic delivery systems. Although the above-described fluids were found to result
17 in osmotic engine freeze-up in the particular system tested, they may be useful in the
18 present invention with osmotic agents other than the one tested. The osmotic agent
19 used in the above described tests was a salt tablet with a gellant, more particularly, a
20 salt tablet with 79.6% NaCl, 12.2% NaCMC, 5.9% Plasdone, 1.7% H₂O, and 0.5%
21 Mg stearate. In general, any combination of osmotic agent and fluid additives
22 which are inert with the membrane, piston, and capsule may be used as long as the
23 osmotic agent does not cause swelling which leads to osmotic agent freeze-up within
24 the capsule, which is easily determined from experimentation.

1 Materials which may be used for the capsule 12 must be sufficiently strong
2 to ensure that the capsule will not leak, crack, break, or distort under stresses to
3 which it would be subjected during implantation or under stresses due to the
4 pressures generated during operation. The capsule 12 may be formed of chemically
5 inert and biocompatible, natural or synthetic materials which are known in the art.
6 The capsule material is preferably a non-bioerodible material which remains in the
7 patient after use, such as titanium. However, the material of the capsule may
8 alternatively be of bioerodible material which bioerodes in the environment after
9 dispensing of the beneficial agent. Generally, preferred materials for the enclosure
10 or capsule 12 are those acceptable for human implants.

11 In general, typical materials of construction suitable for the capsule 12
12 according to the present invention include non-reactive polymers or biocompatible
13 metals or alloys. The polymers include acrylonitrile polymers such as acrylonitrile-
14 butadiene-styrene terpolymer, and the like; halogenated polymers such as
15 polytetrafluoroethylene, polychlorotrifluoroethylene, copolymer tetrafluoroethylene
16 and hexafluoropropylene; polyimide; polysulfone; polycarbonate; polyethylene;
17 polypropylene; polyvinylchloride-acrylic copolymer; polycarbonate-acrylonitrile-
18 butadiene-styrene; polystyrene; and the like. Metallic materials useful for the
19 capsule 12 include stainless steel, titanium, platinum, tantalum, gold, and their
20 alloys, as well as gold-plated ferrous alloys, platinum-plated ferrous alloys, cobalt-
21 chromium alloys and titanium nitride coated stainless steel.

22 In general, materials suitable for use in the piston 22 are elastomeric
23 materials including the non-reactive polymers listed above, as well as elastomers in
24 general, such as polyurethanes and polyamides, chlorinated rubbers, styrene-
25 butadiene rubbers, and chloroprene rubbers.

26 The osmotic tablet 26 is an osmotic agent which is a fluid-attracting agent
27 used to drive the flow of the beneficial agent. The osmotic agent may be an
28 osmagent, an osmopolymer, or a mixture of the two. Species which fall within the
29 category of osmagent, i.e., the non-volatile species which are soluble in water and
30 create the osmotic gradient driving the osmotic inflow of water, vary widely.

1 Examples are well known in the art and include magnesium sulfate, magnesium
2 chloride, potassium sulfate, sodium chloride, sodium sulfate, lithium sulfate, sodium
3 phosphate, potassium phosphate, d-mannitol, sorbitol, inositol, urea, magnesium
4 succinate, tartaric acid, raffinose, and various monosaccharides, oligosaccharides
5 and polysaccharides such as sucrose, glucose, lactose, fructose, and dextran, as well
6 as mixtures of any of these various species.

7 Species which fall within the category of osmopolymer are hydrophilic
8 polymers that swell upon contact with water, and these vary widely as well.
9 Osmopolymers may be of plant or animal origin, or synthetic, and examples of
10 osmopolymers are well known in the art. Examples include: poly(hydroxy-alkyl
11 methacrylates) with molecular weight of 30,000 to 5,000,000,
12 poly(vinylpyrrolidone) with molecular weight of 10,000 to 360,000, anionic and
13 cationic hydrogels, polyelectrolyte complexes, poly(vinyl alcohol) having low
14 acetate residual, optionally cross linked with glyoxal, formaldehyde or
15 glutaraldehyde and having a degree of polymerization of 200 to 30,000, a mixture of
16 methyl cellulose, cross linked agar and carboxymethylcellulose, a mixture of
17 hydroxypropyl methylcellulose and sodium carboxymethylcellulose, polymers of N-
18 vinyl lactams, polyoxyethylene-polyoxypropylene gels, polyoxybutylene-
19 polyethylene block copolymer gels, carob gum, polyacrylic gels, polyester gels,
20 polyurea gels, polyether gels, polyamide gels, polypeptide gels, polyamino acid
21 gels, polycellulosic gels, carbopol acidic carboxy polymers having molecular
22 weights of 250,000 to 4,000,000, Cyanamer polyacrylamides, cross linked indene-
23 maleic anhydride polymers, Good-Rite polyacrylic acids having molecular weights
24 of 80,000 to 200,000, Polyox Polyethylene oxide polymers having molecular
25 weights of 100,000 to 5,000,000, starch graft copolymers, and Aqua-Keeps acrylate
26 polymer polysaccharides.

27 Delivery capsules in accordance with the present invention for the delivery
28 of beneficial agents, may be manufactured by a variety of techniques, many of
29 which are known in the art. In one such technique, the beneficial agent and an
30 osmotically active agent are prepared as solid or semi-solid formulations and pressed

-13-

1 into pellets or tablets whose dimensions correspond to slightly less than the internal
2 dimensions of the respective chambers which they will occupy in the capsule
3 interior. Depending on the nature of the materials used, the two agents and other
4 solid ingredients which may be included with them may be processed prior to the
5 formation of the pellets by such procedures as ballmilling, calendaring, stirring or
6 rollmilling to achieve a fine particle size and hence fairly uniform mixtures of each.
7 The capsule may be formed from any of the wall-forming materials disclosed above
8 by the use of a mold, with the materials applied either over the mold or inside the
9 mold, depending on the mold configuration. In assembling the osmotic delivery
10 device according to one embodiment of the present invention, the piston 22 is first
11 inserted into the capsule 12. Then an osmotic agent 26 is placed in the capsule 12;
12 specifically, once the osmotic pellets or tablets have been formed, they are placed
13 inside the pre-formed capsule with the piston or portion 22. Thereafter, a filler tip
14 of a micro pipet or similar dispenser well known in the art is inserted into the
15 capsule to dispense the fluid additive 30. Where an end cap or membrane plug 28 is
16 a part of the device, such is then placed onto the capsule to close it. Finally, the
17 beneficial agent is inserted into the end of the capsule opposite the plug 28.

18 The capsule orifice 18 or orifices are also formed by conventional techniques
19 which are known in the art. Included among these methods are mechanical drilling,
20 laser drilling, and molding. The capsule will contain at least one such orifice, and
21 in most configurations, one orifice will suffice. However, two or more orifices may
22 be present without departing from the present invention. The dimensions of the
23 orifice in terms of both diameter and length will vary with the type of beneficial
24 agent, the rate at which the beneficial agent is to be delivered, and the environment
25 into which it is to be delivered. The considerations involved in determining the
26 optimum dimensions of the orifice for any particular capsule or beneficial agent are
27 the same as those for orifices of capsules of the prior art, and selection of the
28 appropriate dimensions will be readily apparent to those skilled in the art.

29 In other embodiments of this invention, the beneficial agents contained in the
30 first chamber 20 are flowable compositions such as liquids, suspension, or slurries,

-14-

1 and are poured into the capsule after the osmotic agent and the piston 22 have been
2 inserted. Still further alternatives may include any of the wide variety of techniques
3 known in the art for forming capsules used in the pharmaceutical industry.

4 Animals to whom drugs may be administered using systems of this invention
5 include humans and other animals. The invention is of particular interest for
6 application to humans and household, sport, and farm animals, particularly
7 mammals. For the administration of beneficial agents to animals, the devices of the
8 present invention may be implanted subcutaneously or intraperitoneally wherein
9 aqueous body fluids are available to activate the osmotic engine. Devices of the
10 invention may also be administered to the rumen of ruminant animals, in which
11 embodiment the devices may further comprise a density element for maintaining the
12 device in the rumen for extended periods of time of up to 120 days or longer.
13 Density elements are well known in the art of drug delivery devices.

14 The devices of this invention are also useful in environments outside of
15 physiological or aqueous environments. For example, the devices may be used in
16 intravenous systems (attached to an IV pump or bag or to an IV bottle, for example)
17 for delivering beneficial agents to animals, primarily to humans. They may also be
18 utilized in blood oxygenators, kidney dialysis and electrophoresis, for example.
19 Additionally, devices of the present invention may be used in the biotechnology
20 area, such as to deliver nutrients or growth regulating compounds to cell cultures.
21 In such instances, activating mechanisms such as mechanical mechanisms are
22 particularly useful.

23 The present invention applies to the administration of beneficial agents in
24 general, which include any physiologically or pharmacologically active substance.
25 The beneficial agent may be any of the agents which are known to be delivered to
26 the body of a human or an animal such as medicaments, vitamins, nutrients, or the
27 like. The beneficial agent may also be an agent which is delivered to other types of
28 aqueous environments such as pools, tanks, reservoirs, and the like. Included
29 among the types of agents which meet this description are biocides, sterilization

1 agents, nutrients, vitamins, food supplements, sex sterilants, fertility inhibitors and
2 fertility promoters.

3 Drug agents which may be delivered by the present invention include drugs
4 which act on the peripheral nerves, adrenergic receptors, cholinergic receptors, the
5 skeletal muscles, the cardiovascular system, smooth muscles, the blood circulatory
6 system, synaptic sites, neuroeffector junctional sites, endocrine and hormone
7 systems, the immunological system, the reproductive system, the skeletal system,
8 autacoid systems, the alimentary and excretory systems, the histamine system and
9 the central nervous system. Suitable agents may be selected from, for example,
10 proteins, enzymes, hormones, polynucleotides, nucleoproteins, polysaccharides,
11 glycoproteins, lipoproteins, polypeptides, steroids, analgesics, local anesthetics,
12 antibiotic agents, anti-inflammatory corticosteroids, ocular drugs and synthetic
13 analogs of these species.

14 Examples of drugs which may be delivered by devices according to this
15 invention include, but are not limited to prochlorperazine edisylate, ferrous sulfate,
16 aminocaproic acid, mecamylamine hydrochloride, procainamide hydrochloride,
17 amphetamine sulfate, methamphetamine hydrochloride, benzamphetamine
18 hydrochloride, isoproterenol sulfate, phenmetrazine hydrochloride, bethanechol
19 chloride, methacholine chloride, pilocarpine hydrochloride, atropine sulfate,
20 scopolamine bromide, isopropamide iodide, tridihexethyl chloride, phenformin
21 hydrochloride, methylphenidate hydrochloride, theophylline choline, cephalixin
22 hydrochloride, diphenidol, meclizine hydrochloride, prochlorperazine maleate,
23 phenoxybenzamine, thiethylperazine maleate, anisindone, diphenadione erythrityl
24 tetranitrate, digoxin, isofluorophate, acetazolamide, methazolamide,
25 bendroflumethiazide, chloropromazine, tolazamide, chlormadinone acetate,
26 phenaglycodol, allopurinol, aluminum aspirin, methotrexate, acetyl sulfisoxazole,
27 erythromycin, hydrocortisone, hydrocorticosterone acetate, cortisone acetate,
28 dexamethasone and its derivatives such as betamethasone, triamcinolone,
29 methyltestosterone, 17-S-estradiol, ethinyl estradiol, ethinyl estradiol 3-methyl

1 ether, prednisolone, 17 α -hydroxyprogesterone acetate, 19-nor-progesterone,
2 norgestrel, norethindrone, norethisterone, norethiederone, progesterone,
3 norgesterone, norethynodrel, aspirin, indomethacin, naproxen, fenoprofen,
4 sulindac, indoprofen, nitroglycerin, isosorbide dinitrate, propranolol, timolol,
5 atenolol, alprenolol, cimetidine, clonidine, imipramine, levodopa, chlorpromazine,
6 methyl dopa, dihydroxyphenylalanine, theophylline, calcium gluconate, ketoprofen,
7 ibuprofen, cephalexin, erythromycin, haloperidol, zomepirac, ferrous lactate,
8 vincamine, diazepam, phenoxybenzamine, diltiazem, milrinone, capropril, mandol,
9 quanbenz, hydrochlorothiazide, ranitidine, flurbiprofen, fenufen, fluprofen,
10 tolmetin, alclofenac, mefenamic, flufenamic, difuinal, nimodipine, nitrendipine,
11 nisoldipine, nicardipine, felodipine, lidoflazine, tiapamil, gallopamil, amlodipine,
12 mioflazine, lisinopril, enalapril, enalaprilat, captopril, ramipril, famotidine,
13 nizatidine, sucralfate, etintidine, tetratolol, minoxidil, chlordiazepoxide, diazepam,
14 amitriptyline, and imipramine. Further examples are proteins and peptides which
15 include, but are not limited to, insulin, colchicine, glucagon, thyroid stimulating
16 hormone, parathyroid and pituitary hormones, calcitonin, renin, prolactin,
17 corticotrophin, thyrotropic hormone, follicle stimulating hormone, chorionic
18 gonadotropin, gonadotropin releasing hormone, bovine somatotropin, porcine
19 somatotropin, oxytocin, vasopressin, GRF, prolactin, somatostatin, lyppressin,
20 pancreozymin, luteinizing hormone, LHRH, LHRH agonists and antagonists,
21 leuprolide, interferons, interleukins, growth hormones such as human growth
22 hormone, bovine growth hormone and porcine growth hormone, fertility inhibitors
23 such as the prostaglandins, fertility promoters, growth factors, coagulation factors,
24 human pancreas hormone releasing factor, analogs and derivatives of these
25 compounds, and pharmaceutically acceptable salts of these compounds, or their
26 analogs or derivatives.

27 The beneficial agent can be present in this invention in a wide variety of
28 chemical and physical forms, such as solids, liquids and slurries. On the molecular
29 level, the various forms may include uncharged molecules, molecular complexes,

1 and pharmaceutically acceptable acid addition and base addition salts such as
2 hydrochlorides, hydrobromides, sulfate, laurylate, oleate, and salicylate. For acidic
3 compounds, salts of metals, amines or organic cations may be used. Derivatives
4 such as esters, ethers and amides can also be used. An active agent can be used
5 alone or mixed with other active agents.

6 According to other embodiments of the present invention, the capsule 12
7 may take different forms. For example the membrane plug 28 may be eliminated
8 and the walls of the second chamber 24 itself may be formed of a membrane
9 material. The fluid delivery orifice 18 may be a soft impermeable material. In
10 addition, the piston 22 may be replaced with a flexible member such as a
11 diaphragm, partition, pad, flat sheet, spheroid, or rigid metal alloy, and may be
12 made of any number of inert materials. Furthermore, the osmotic device may
13 function without the piston 22, having simply an interface between the osmotic
14 agent/fluid additive and the beneficial agent.

15 While the invention has been described in detail with reference to a preferred
16 embodiment thereof, it will be apparent to one skilled in the art that various changes
17 can be made, and equivalents employed without departing from the spirit and scope
18 of the invention.

1 WHAT IS CLAIMED IS:

2 1. An osmotic drug delivery device comprising:
3 a capsule including a first chamber for containing a beneficial agent
4 and a second chamber;
5 an osmotic agent located within the second chamber;
6 a wall of the second chamber including a fluid permeable portion
7 allowing fluid to pass from a surrounding environment into the second chamber; and
8 an incompressible fluid additive within the second chamber
9 substantially surrounding the osmotic agent.

10

11 2. The osmotic drug delivery device according to claim 1, further
12 comprising a movable separating member positioned in the capsule between the first
13 chamber and the second chamber.

14

15 3. The osmotic drug delivery system according to claim 2, wherein the
16 separating member is a slidable piston.

17

18 4. The osmotic drug delivery device according to claim 1, wherein the
19 fluid permeable portion is a membrane.

20

21 5. The osmotic drug delivery device according to claim 1, wherein the
22 osmotic agent is a tablet.

23

24 6. The osmotic drug delivery device according to claim 1, wherein the
25 fluid additive is a lubricating liquid for preventing freeze-up of the osmotic agent.

26

27 7. The osmotic drug delivery device according to claim 1, wherein the
28 fluid additive is a gel.

29

1 8. The osmotic drug delivery device according to claim 1, wherein the
2 fluid additive is one of PEG 400, PEG 1000, propylene glycol, CMC in water,
3 polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate, PG,
4 DMSO, and peanut oil.

5
6 9. The osmotic drug delivery system according to claim 1, including at
7 least one gap between an inner surface of the capsule and the osmotic agent, said
8 fluid additive filling the at least one gap to improve start-up time.

9
10 10. An osmotic drug delivery device comprising:
11 an enclosure holding an osmotic agent which imbibes fluid from a
12 surrounding environment and swells to cause delivery of a beneficial agent; and
13 an incompressible fluid filler located within the enclosure and at least
14 partially surrounding the osmotic agent.

15
16 11. The osmotic drug delivery device according to claim 10, wherein the
17 enclosure includes a first chamber for containing the beneficial agent and a second
18 chamber, the second chamber containing the osmotic agent and the fluid filler.

19
20 12. The osmotic drug delivery device according to claim 11, wherein the
21 first chamber and the second chamber are separated by a partition.

22
23 13. The osmotic drug delivery system according to claim 12, wherein the
24 partition is a slidable piston.

1 14. The osmotic drug delivery device according to claim 10, wherein the
2 fluid filler is a lubricating liquid.

3
4 15. The osmotic drug delivery device according to claim 10, wherein the
5 fluid filler is a gel.

6
7 16. The osmotic drug delivery device according to claim 10, wherein the
8 fluid filler is one of PEG 400, PEG 1000, propylene glycol, CMC in water,
9 polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate, PG,
10 DMSO, and peanut oil.

11
12 17. The osmotic drug delivery system according to claim 10, including at
13 least one gap between an inner surface of the enclosure and the osmotic agent,
14 wherein the fluid filler fills the at least one gap.

15
16 18. The osmotic drug delivery system according to claim 10, wherein the
17 fluid filler is an osmotic agent.

18
19 19. The osmotic drug delivery system according to claim 10, wherein the
20 osmotic agent is a tablet.

21
22 20. The osmotic drug delivery system according to claim 10, wherein the
23 osmotic agent is a fluid swellable material causing delivery of the beneficial agent at
24 a controlled rate.

25
26 21. A method of improving start-up time of an osmotic drug delivery
27 system that includes an enclosure, an osmotic agent provided within the enclosure,
28 and a gap between an inner surface of the enclosure and an outer surface of the
29 osmotic agent, comprising the step of removing gas between the outer surface of the

-21-

- 1 osmotic agent and the inner surface of the enclosure by providing an incompressible
- 2 fluid in the gap.

1 / 3

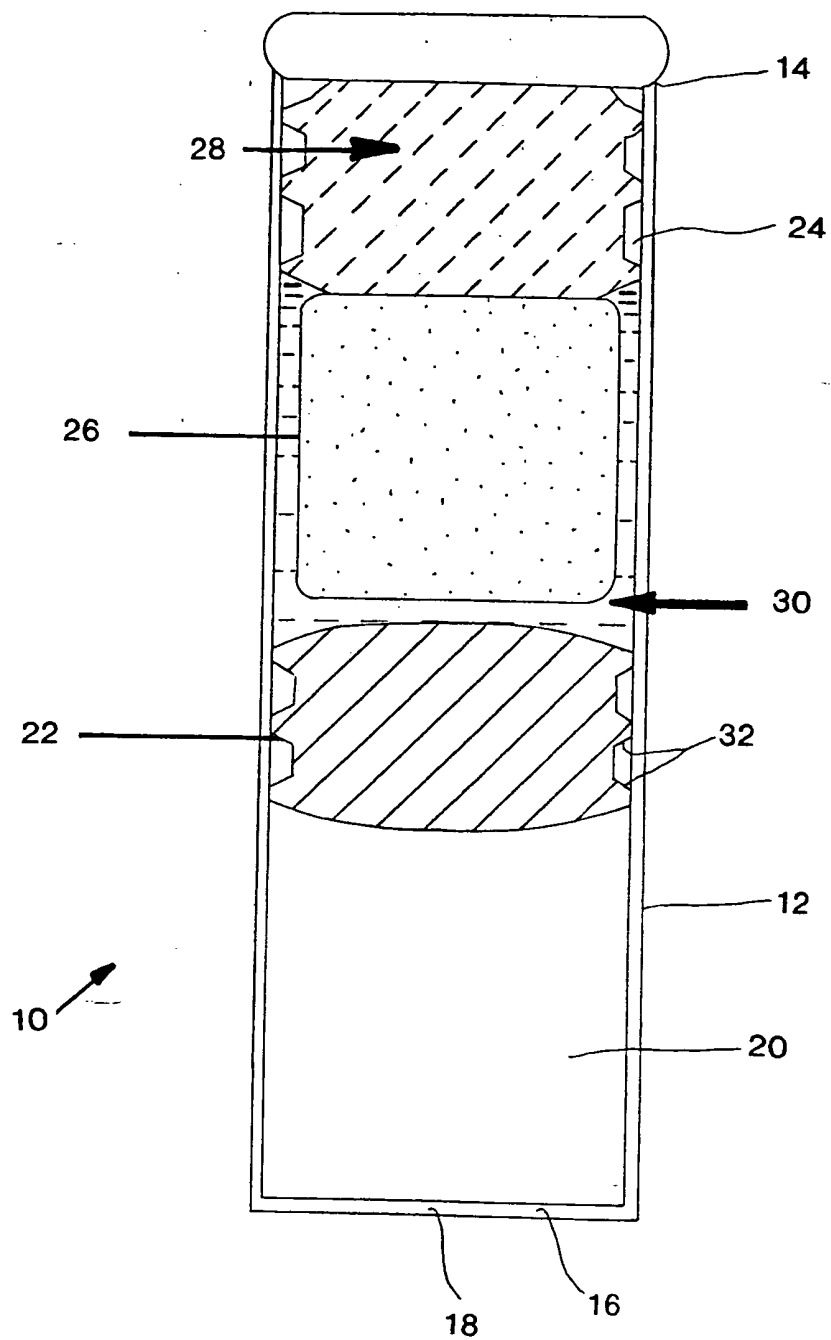


FIG. 1

2 / 3

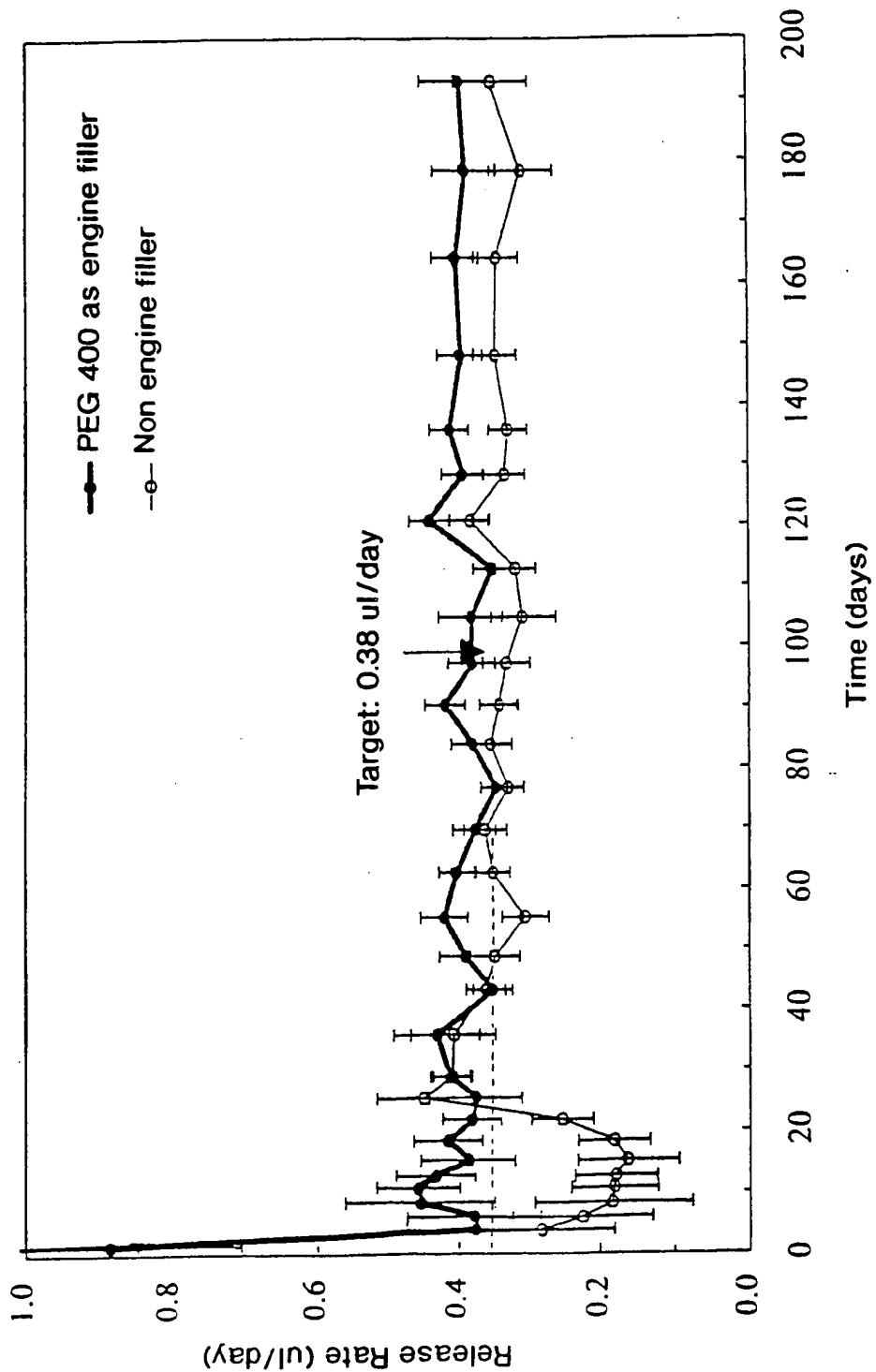


FIG. 2

3 / 3

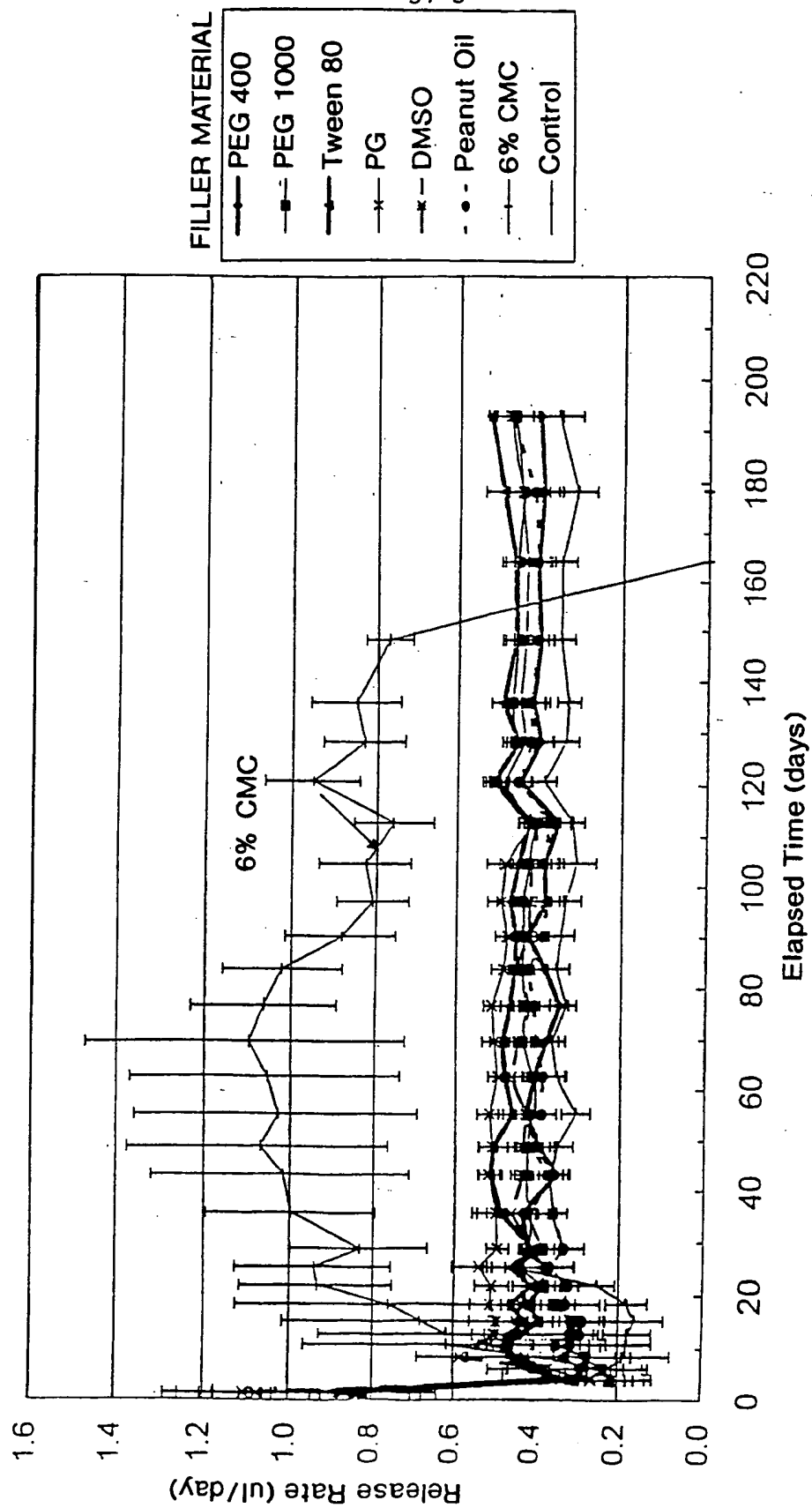


FIG. 3

INTERNATIONAL SEARCH REPORT

In: .tional Application No

PCT/US 97/20480

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61M31/00

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 456 679 A (BALABAN ET AL.) 10 October 1995 cited in the application see abstract see column 2, line 57 - column 3, line 53; claims 1,4-6; figures 1,4	1-21
A	US 4 915 954 A (AYER ET AL.) 10 April 1990 see column 2, line 47 - line 52 see column 3, line 17 - line 22 see column 4, line 30 - line 53; figures 1,2	1-21
A	EP 0 373 867 A (ALZA CORPORATION) 20 June 1990 cited in the application see abstract; claims 1,2,4-6,10; figures 1,8	1-21
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

26 February 1998

Date of mailing of the international search report

09/03/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5618 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epc nl.
Fax: (+31-70) 340-3016

Authorized officer

Michels, N

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 97/20480

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 318 558 A (LINKWITZ ET AL.) 7 June 1994 see abstract; claim 1; figure 1; example 1 -----	1-21

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/20480

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5456679 A	10-10-95	US 5308348 A US 5209746 A EP 0627231 A MX 9300879 A ZA 9301140 A	03-05-94 11-05-93 07-12-94 01-08-93 01-11-93
US 4915954 A	10-04-90	US 4814181 A AT 400296 B AT 214488 A AU 2152688 A BE 1001184 A CA 1288016 A CH 676794 A DE 3829942 A DK 485588 A FR 2620025 A GB 2209280 A, B IE 61845 B JP 1096116 A KR 9506216 B LU 87326 A NL 8802180 A NO 176902 B SE 8803084 A US 4915953 A	21-03-89 27-11-95 15-04-95 09-03-89 08-08-89 27-08-91 15-03-91 16-03-89 04-03-89 10-03-89 10-05-89 30-11-94 14-04-89 12-06-95 08-03-89 03-04-89 13-03-95 04-03-89 10-04-90
EP 0373867 A	20-06-90	US 5034229 A AU 633514 B AU 4247889 A CA 1331328 A DE 68910290 D DE 68910290 T DK 624589 A ES 2045474 T IE 62142 B JP 2184619 A JP 2532692 B NO 174878 B US 5630808 A US 5174999 A	23-07-91 04-02-93 21-06-90 09-08-94 02-12-93 17-02-94 14-06-90 16-01-94 14-12-94 19-07-90 11-09-96 18-04-94 20-05-97 29-12-92

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/20480

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0373867 A		US 5057318 A	15-10-91
		US 5037420 A	06-08-91
		US 5110596 A	05-05-92
		US 5135523 A	04-08-92
		US 5059423 A	22-10-91
		US 5714160 A	03-02-98
		US 5320616 A	14-06-94
<hr/>			
US 5318558 A	07-06-94	US 5221278 A	22-06-93
<hr/>			